REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

Independent claims 24, 28, 49 and 50 are currently amended above to clarify that the claimed invention is directed toward a method of treating "hormonal dependent benign or malignant disease of the breast or reproductive tract" pursuant to the Examiner's suggestion at page 2 of the Action. Support for this amendment is found throughout the specification, *e.g.*, at page 2, lines 9-18 and page 16, lines 4-5.

Claim 32 is currently amended above to clarify that the 17-23% refers to "w/v of a pharmaceutically acceptable alcohol." The need for this correction and the nature thereof is readily apparent from claim 29, upon which claim 32 is dependent.

No new matter is added by the above amendments, and entry thereof is believed to be in order and is respectfully requested. Following entry of these amendments, claims 24-50 remain pending in this application.

Claim Objections

The informality objection to claim 32 as lacking a period has been corrected and overcome by the above amendment to claim 32.

Claim Rejections – 35 USC § 112

Claims 24-50 have been rejected under 35 USC § 112, first paragraph, as lacking enablement. Specifically, the Examiner notes that the specification, "while being enabling for cancer and certain hormonal-dependent benign diseases of the breast and endometrial lining, does not reasonably provide enablement for other non-hormonal dependent conditions of the breast and the reproductive tract." This ground for rejection has been specifically addressed and overcome by amending each dependent claims (and therefore each claim dependent thereon) to specifically recite that the method of treatment applies to "hormonal dependent benign or malignant disease of the breast or reproductive tract." Withdrawal of this ground for rejection is therefore respectfully requested.

Claim Rejections – 35 USC § 103

Claims 24-50 have been rejected under 35 USC § 103(a) as being unpatentable over Dukes, EP 0 346 014 (hereinafter "Dukes") in view of Lehmann *et al*, US Patent Re 28,690 (hereinafter "Lehmann") , GB 1 569 286 (hereinafter "GB '286), and Remington's Pharmaceutical Sciences (hereinafter "Remington").

In applying the primary Dukes reference, the Examiner notes:

> Dukes teaches antiestrogen agents, including fulvestrant, are useful in treating postmenopausal symptoms such as urogenital atrophy affecting the vagina (See page 3, lines 56-page 4, line 1; also page 7, line 28-29). Dukes teaches that antiestrogen agent, including fulvestrant, may be used in a dosage of 50mg to 5g in vehicle comprising castor oil and benzyl alcohol (See page 7, 20-24).

(Action at page 5). The Examiner acknowledges in the following paragraph, however, that Dukes does not expressly teach the dosage of fulvestrant, the formulation and/or plasma concentration of fulvestrant as recited in the present claims. The Examiner attempts to fill the

acknowledged gaps in the Dukes disclosure with the secondary references, specifically noting:

> Lehman et al. teaches that benzyl benzoate and caster oil are well-known solvent useful as conventional carriers for steroids (See col. 1, line 21-26).
> '286 teaches an intramuscular injection of testosterone derivative containing castor oil/benzoate in the ratio of 6:4 (See page 1, line 17).
> Remington teaches that ethanol is one of the most commonly used solvents in pharmaceutical industry (See page 219).

(Action page 6). From a combination of these references, the Examiner concludes:

> Therefore, combining one or more agents, which are known to be useful as commonly used solvents, such as benzyl benzoate, ethanol, castor oil, and benzyl alcohol, together and incorporated such combination with an estrogen derivatives, fulvestrant, would be reasonably expect to be useful in formulating a pharmaceutical composition. Furthermore, employing such fulvestrant-containing composition to treat urogenital atrophy in vagina would be reasonably expected to be effective. Moreover, the optimization of result effect parameters (e.g., amount of excipients, dosage range, and dosing regimens) is obvious as being within the skill of the artisan.
> One of ordinary skill in the art would have been motivated to maintain the plasma concentration of fulvestrant herein because maintaining the therapeutic plasma level of the active compounds would be considered obvious as being within the purview of the skilled artisan.

(Action page. 7).

Applicants respectfully disagree.

Applicants recognize in their specification at page 3 and in Table I that sustained release injectable steroidal formulations are known (and commercialized) using various oils to solubilize the compound and additional excipients such as benzyl benzoate, benzyl alcohol and ethanol. However, as also noted at page 3, lines 4-7, fulvestrant (to which the presently claimed invention is specifically directed) is a *particularly* lipophilic molecule, even when compared with other steroidal compounds, and has an *extremely* low aqueous solubility of

around 10 $ngml^{-1}$.[1] In their quest for an appropriate injection vehicle for fulvestrant, applicants found that fulvestrant is significantly more soluble in castor oil than any of the other oils tested, as noted at page 6 of the specification and in Table 2. They acknowledge that the greater solvating ability of castor oil for steroidal compounds is known, and is attributed to the high number of hydroxyl groups of ricinoleic acid present in castor oil, citing Riffkin (1964).[2] Nevertheless, applicants found that it was not possible to dissolve fulvestrant in castor oil alone so as to achieve a high enough concentration to dose a patient in an acceptably low volume injection and still achieve a therapeutically significant release rate (specification pages 6-7). Even with the prior art disclosures of additionally using various alcohols and esters, applicants were faced with a particularly difficult problem resulting from the very low solubility of fulvestrant that was not specifically addressed by the prior art.

Again, it should be borne in mind that the claims are drawn to the *single pharmaceutical agent, fulvestrant.* In this regard, the Examiner cites Dukes as the primary reference as teaching that antiestrogen agents, including fulvestrant, may be used in a dosage of 50mg to 5g in vehicle comprising castor oil and benzyl alcohol. However, Dukes lists an enormous number of possible formulations, including tablets and capsules for oral administration, aqueous suspensions of the active ingredient in finely powdered form, oily suspensions, dispersible powders, oil-in-water emulsions, injectable aqueous or oily suspensions, including in the form of a depot of the active ingredients at the injection site to

[1] This solubility had to be estimated from a water/solvent mixture solute since measurements this low could not be achieved in a water only solute (specification at page 3, lines 6-7.

[2] Riffkin et al., "Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones", Journal of Pharmaceutical Sciences, Vol. 53, No. 8, August 1964, pp. 891-895; cited at specification page 6, lines 14-15, and as Reference NR on page 3 of the form PTO-1449 submitted with the Information Disclosure Statement filed herein on February 1, 2002.

provide the sustained release thereof, suppository formulations and topical formulations; see the text from page 4, line 28 to page 5, line 36. Dukes does not suggest that there are any problems with fulvestrant in these formulations. Example 3 of Dukes discloses a castor oil formulation for intramuscular injection consisting of fulvestrant 50mg/ml, benzyl alcohol (40 %) administered at 2 weekly intervals. Again, Dukes does not suggest that there are any problems with this formulation. Example 2 of Dukes uses a propylene glycol based intramuscular injection of fulvestrant, and again Dukes does not suggest that there are any problems with this formulation.

Therefore Dukes does not suggest that there would be any problem using fulvestrant in any of these formulations, and does not even express a preference for castor oil based intramuscular formulations over other injectable formulations of fulvestrant in general, let alone the particular castor oil based formulations having the features of the presently claimed invention. Accordingly, there is no motivation to move on from Dukes.

In particular, persons skilled in the art would have no motivation to combine Dukes with the disclosures of Lehmann or GB '286, as asserted by the Examiner. Fulvestrant is a very different pharmaceutical agent from the agents described in Lehmann and GB '286 patent for the following reasons.

These citations all relate to formulated *prodrugs* (not drugs *per se*) in the form of drug esters. Fulvestrant is not a prodrug and a skilled person working with fulvestrant drug would not turn to such citations for teaching relevant to fulvestrant *per se,* which is not amenable to such prodrug formulation.

Esterification of readily soluble base drugs with lipophilic fatty acids forms a prodrug ester whose hydrophobic side chains partition preferentially into the oil vehicle.

Prolongation of prodrug release is provided by rate limiting diffusion of prodrug into extracellular fluid where various esterases liberate active drug. As explained in Mackey (1995),[3] a copy of which is included with the further Information Disclosure Statement submitted herewith:

> Depot formulations are widely used to enhance therapeutic compliance and convenience by prolonging the duration of drug action. Among the most widely used depot formulations are drug esters administered in an oil vehicle. Esterification of base drugs with appropriate lipophilic fatty acids forms a pro-drug ester whose hydrophobic side-chains partition preferentially into the oil vehicle. Prolongation of the pro-drug release is provided by the rate-limiting retarded diffusion of the pro-drug ester into the extracellular fluid where ubiquitous non-specific esterases hydrolyse the ester bond to liberate active drug. In addition to forming a hydrophobic depot, the oil vehicle limits local chemical irritation and cytotoxicity caused by some drugs (Svendsen and 'Blom, 1984). This oil-based formulation has been widely and successfully used for sex steroids including androgens, oestrogens and progestins as well as psychotrophic drugs such as fluphenazine, haloperidol and related major tranquilizers (Gilman *et al.,* 1990). Oils derived from vegetable sources such as castor or sesame seeds or peanuts (*Arachis*) have been widely used whereas mineral oils are too irritating (Symmers, 1955).

(Mackey at pages 863-864 under "Discussion"; emphasis added)

Mackey continues at the top of page 863, "(t)estosterone esters in an oil vehicle have been for decades the most widely used modality of delivering androgen replacement therapy in male hypogonadism" (emphasis added). Similarly, steroidal ester prodrugs in an oil vehicle are disclosed in Lehmann (diesters of nortestosterone in a variety of vegetable oils including caster oil, as well as various synthetic solvents including benzyl benzoate) and GB '286 ((norethisterone oenanthate in a mixture of castor oil/benzyl benzoate). See, also, Riffkin (1964), *supra*, disclosing 17-hydroxyprogesterone caproate and estradiol valerate in

[3] Mackey *et al.*, "Tolerability of intramuscular injections of testosterone ester in oil vehicle," Human Reproduction, 1995, vol. 10 no. 4, pp. 862-895.

various oil vehicles (including caster oil) with various cosolvents (including benzyl alcohol and benzyl benzoate).

As well as not being amenable to the prodrug approach, fulvestrant has very different chemical properties in terms of its markedly lower water solubility compared with the drugs disclosed in these references. Even if formulated in oils, water solubility is one of the principal factors governing release and bioavailability from any formulation.

For example, the drugs of Lehmann and GB '286 are suitable for oral administration and are converted into a *less hydrophilic* prodrug form to allow formulation in a oily depot. Given the already low water solubility of fulvestrant, it would simply not make sense for a skilled person to make it into an even less water soluble prodrug.

Lehmann states that the relevant prodrug compounds are "readily soluble" (col 1, line 21) and refers to their "considerable solubility" (col 1, line 27). These prodrug compounds are said to be readily soluble in a wide range of vegetable oils and synthetic solvents (col 1, lines 23-26). In contrast, fulvestrant is significantly more soluble in castor oil (20 mg/ml) compared with other oils tested (see Table 2 of the specification). Lehman lists benzyl benzoate as a synthetic solvent in which the prodrugs are "readily soluble" whereas the solubility of fulvestrant in benzyl benzoate is only 6.15 mg/ml (again see Table 2 of the specification).

A specific example in the '286 patent uses 200 mg of prodrug (norethisterone oenanthate) in as little as 0.6 ml of castor oil/ benzyl benzoate (6:4) – see page 1, lines 27-29. This formulation would simply not work for fulvestrant.

Therefore a skilled person starting from Dukes would not turn to the injectable vehicles of Lehmann or GB '286 patent, or Riffkin, to improve upon the formulations disclosed in Dukes with respect to fulvestrant.

Finally, Remington simply teaches in the abstract, and unrelated to injectable oil vehicles for steroidal compounds, that "*(e)thanol*, as a solvent, is next in importance to water." This reference provides no teaching specifically relevant to formulation of fulvestrant, and does not overcome the shortcomings of the combination of the other references as discussed above.

As discussed above, the primary Dukes references teaches antiestrogen agents, including fulvestrant, in a great variety of modes of administration and vehicles, including in a vehicle comprising caster oil and benzyl alcohol. However, as the Examiner notes at page 5 of the Action, Dukes does not teach the inclusion of benzyl benzoate in such vehicle. In fact, Dukes does not teach the inclusion of any "pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle" in context of fulvestrant. Although other references cited by the Examiner and/or noted above teach various combinations of oil, alcohol and/or ester, these references would not suggest to persons skilled in the art the modification of the Dukes teaching by addition of such a "pharmaceutically-acceptable non-aqueous ester solvent miscible in a ricinoleate vehicle" in formulations of fulvestrant, for the reasons detailed above. In particular, there is no motivation in Dukes to modify the formulation of Example 3 by including an ester solvent, particularly as fulvestrant is less soluble in esters than in alcohols.

A person of ordinary skill would always measure solubility of fulvestrant in a vehicle component before using it. Example 3 of Dukes discloses a castor oil formulation for

intramuscular injection consisting of fulvestrant 50mg/ml, benzyl alcohol (40 %). Looking at Table 2 in the specification, the solubility of fulvestrant in benzyl alcohol is over 200mg/ml. A non-aqueous ester solvent such as benzyl benzoate gives a solubility of fulvestrant of only 6.15 mg/ml. Upon making such a determination, the observed low solubility of the ester would teach a person of ordinary skill not to use it further in the formulation. However, when the inventors included ester solvent in lieu of part of the alcohol component, they observed the following:

> We have surprisingly found that the introduction of a non-aqueous ester solvent which is miscible in the castor oil and an alcohol surprisingly eases the solubilisation of fulvestrant into a concentration of at least 50 $mgml^{-1}$ - see Table 3 below. The finding is surprising since the solubility of fulvestrant in non-aqueous ester solvents - see Table 2 above - is significantly lower than the solubility of fulvestrant in an alcohol. The solubility of fulvestrant is also lower in non-aqueous ester solvents than is the solubility of fulvestrant in castor oil.

(Specification page 7, lines 13-18).

In other words, looking at Table 3 of the specification and comparing the data in column pairs across the page, it is evident that inclusion of ester (benzyl benzoate) increases the solubility of fulvestrant in the formulation. For example, looking at columns 1 and 2, the addition of ester to the formulation increases the solubility of fulvestrant from 27 mg/ml to 36 mg/ml. This is unexpected because Table 2 shows us that non-aqueous ester solvent such as benzyl benzoate gives a solubility of fulvestrant of only 6.15 mg/ml.

Thus, persons of ordinary skill in this art, starting from the Dukes disclosure with respect to fulvestrant, would not be motivated to draw from the teachings of the secondary references, which teach or strongly favor the use of ester prodrugs of the steroidal compounds they employ, which are significantly more water soluble than fulvestrant. The particularly lipophilic fulvestrant is not amenable to such prodrug formulation, as discussed

above. Moreover, even if such skilled person were to explore the possibility of substituting an ester such as benzyl benzoate for a portion of the alcohol component of Dukes, they would have been put off from doing so when they appreciated the very low solubility of fulvestrant in such ester. Applicants' discovery of the surprising synergistic effect from the introduction of such a non-aqueous ester solvent which is miscible in the caster oil and an alcohol on easing the solubilization of fulvestrant in castor oil further heightens the unobviousness of the present claims.

Information Disclosure Statement

A further Information Disclosure Statement is submitted herewith, together with a form PTO-1449 formally citing the Mackey *et al.* article noted above and a copy of the cited article. Also, for clarification, it is assumed that the Examiner's statement at page 2 of the action that "the IDS received September 13, 2002 [has] been considered" refers to both Information Disclosure Statements submitted (received) on September 13, 2002, in that both are specifically referred to on page 6 of the Amendment and Response filed September 13, 2002, and a search of the PAIR database confirms that both were separately received and entered into the file by the US Patent and Trademark office on that date.

Conclusion

In view of the above amendments and the foregoing remarks, it is believed that all grounds for rejection have been addressed and overcome. Therefore, withdrawal of the rejections and allowance of all claims are believed to be in order and are respectfully requested.

Respectfully Submitted,
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